

### REMARKS

Claims 1, 3, 4, 6-13, 17, 19, 20, and 22-25 were previously pending, of which claims 1, 3, 4, 6, 10-13, 17, 19, 20, and 22-25 were under examination. By this Amendment claims 1, 4, 6, 13, 17, 20, and 22-25 are currently amended, new claim 38 is added, and no claims are canceled. Upon entry of this Amendment, claims 1, 3, 4, 6, 10-13, 17, 19, 20, 22-25, and 38 are pending and under examination. Claims 7-9 remain pending but withdrawn from consideration. No new matter has been introduced.

Claims 1 and 17 are currently amended to specify that the antibody is an apoptosis-inducing anti-PSGL-1 antibody, and to substitute "apoptosis" of the T cell (or NK cell) for "a signal transduction pathway that results in the death" of the T cell (or NK cell).

Claims 4 and 20 are currently amended to omit "the" from before "cross-linking".

Claim 6 is currently amended to substitute "wherein the condition characterized by an excessive or unwanted T cell-mediated immune response is" an autoimmune disease for "comprising selecting an individual diagnosed as having" an autoimmune disease.

Claims 13 and 25 are currently amended to specify the method is one "further comprising" the recited step or steps, and to amend definite and indefinite articles.

Claims 22-24 are currently amended to substitute the "T cell or NK" cell for the "cell".

New claim 38 depends from claim 17 and specifies the T cell or NK cell is an NK cell.

### Priority

In item number 3 beginning on page 2 of the Office Action the Examiner maintained his previous assertion that the provisional priority application USSN 60/310196, filed on August

3, 2001, does not provide sufficient written description for the claimed limitations of the instant claims. The Examiner indicated that the detailed analysis of support for the currently claimed subject matter found in the provisional application, as set forth by Applicant in the Amendment filed May 30, 2006, was acknowledged but deemed unconvincing to the Examiner. More particularly, the Examiner stated on page 3 of the Office Action that Applicant has *not* presented a detailed analysis as to why the claimed subject matter has clear support in the parent application, other than to assert that the provisional application provides ample written description for each and every limitation as presented and citing certain passages of the provisional application without sufficiently pointing out written support for the “limitations” [original emphasis]. The Examiner concluded by inviting Applicant to verify the priority date of the instant claims, including written support and enablement under 35 USC 112, first paragraph. Applicant respectfully disagrees and requests the Examiner to reconsider and acknowledge benefit of the claimed priority document.

Applicant respectfully points out to the Examiner that many of the “limitations” allegedly lacking support in the priority document concern *original* claims or claim limitations that were canceled or amended by one or more previous amendments. For example, the “limitations” concerning “methods of preventing or reducing a T cell-mediated immune response in an individual”, including the “selecting an individual diagnosed”, “administering a compound ... induces a signal transduction pathway that results in the death of the T cell” (claim 1), relate to claim 1 as originally filed rather than claim 1 as amended on or prior to May 30, 2006. More specifically, “methods of preventing or reducing a T cell-mediated immune response in an individual” was previously amended to read as “A method of reducing a T cell-mediated immune response in an individual”; “selecting an individual diagnosed” was previously amended to read as “diagnosed as having”; and “administering a compound ... induces a signal transduction pathway that results in the death of the T cell” was previously amended to read as “administering to the individual a composition comprising an effective amount of an antibody or antigen-binding fragment thereof ... induces a signal transduction pathway that results in the death of the T cell”.

As a further example, the “limitation” concerning “an agent that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of the T cell” (claim 4) was previously amended to read as “an antibody that binds to the monoclonal antibody and induces the cross-linking of a plurality of PSGL-1 antigens on the surface of the T cell”.

As yet a further example, the “limitation” concerning “20% of peripheral blood CD3<sup>+</sup> cells” (claims 15-16) concern claims that were canceled in the amendment filed January 25, 2005.

In addition to the recitation of support for the claims currently under examination provided in the amendment filed May 30, 2006, Applicant points out the following. As concerns the limitation of “detecting the number of T cells in a first biological sample” in currently pending claim 13, Applicant respectfully submits that Example 6 in the provisional application, and likewise Example 6 in the instant application, in each instance concerning depletion of T cells in vivo, clearly describes administering anti-PSGL antibody TAB4 to experimental mice, harvesting spleens (and peripheral blood leukocytes) six days later, measuring the percentage of CD3<sup>+</sup> T cells in the harvested spleens and peripheral blood, and *comparing these results with corresponding results from untreated mice*. Applicant respectfully submits that this comparison of untreated control mice and treated experimental mice is tantamount to what is claimed in claim 13, i.e., detecting the number of T cells in a first biological sample before administration (of antibody) and comparing the result with the number of T cells in a second biological sample obtained after administration (of antibody).

Further in addition to the recitation of support for the claims currently under examination provided in the amendment filed May 30, 2006, as concerns the limitation “diabetes”, Applicant refers the Examiner to page 15, lines 14-20 of the provisional application, where conditions that can be treated with the anti-TAIP compounds (e.g., anti-PSGL-1 antibodies) described in the application are specifically disclosed to include diabetes mellitus.

Short of any more specific objections by the Examiner, Applicant respectfully submits it has reasonably met its burden in pointing out location of support in the provisional application for the current claim limitations, and, accordingly, Applicant respectfully requests the Examiner to acknowledge Applicant's entitlement to the claimed priority date of August 3, 2001.

**Rejection Under 35 U.S.C. 112, First Paragraph (New Matter)**

In item number 4 beginning on page 4 of the Office Action the Examiner maintained his previous rejection of claims 4 and 20 under 35 U.S.C. 112, first paragraph, because the specification allegedly does not contain a written description of the claimed invention. The Examiner asserts that these claims, directed in pertinent part to an *antibody* that binds to the monoclonal antibody and induces [the] cross-linking of a plurality of PSGL-1 antigen on the surface of the T cell, is supported only by disclosure of the anti-hamster Ig in Example 3 as a cross-linker antibody. The Examiner further asserts that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. Applicant respectfully disagrees and requests the Examiner to reconsider and withdraw this rejection of claims 4 and 20 under 35 U.S.C. 112, first paragraph.

Applicant agrees that claims 4 and 20 as currently amended are directed in pertinent part to an *antibody* that binds to the monoclonal antibody and induces cross-linking of a plurality of PSGL-1 antigens on the surface of the T cell (or the surface of the T cell or NK cell, in claim 20). Applicant also agrees that Example 3 discloses an anti-hamster Ig as a cross-linking antibody as claimed. Applicant wishes to point out to the Examiner that Example 10 discloses another antibody, viz., cross-linker rabbit anti-mouse Ig, that binds to the monoclonal antibody and induces cross-linking of a plurality of PSGL-1 antigens on the surface of the T cell or NK cell. Thus the examples disclose not one but two examples of cross-linking antibody as claimed. Furthermore, the current written description requirement for antibodies is satisfied without necessarily requiring detailed description of the structure or amino acid sequence of said antibodies. It will be appreciated, then, that the claimed genus of cross-linking antibodies includes any suitable anti-isotype antibody, examples of which are so numerous in the prior art

as not to require specific disclosure. For example, if the monoclonal antibody is an IgG antibody, then the cross-linking antibody is reasonably expected to include any anti-IgG antibody that is specific for antigen-non-specific epitope of the monoclonal IgG, e.g., any portion of constant heavy chain or portion of Fc gamma that is relevant to the monoclonal IgG. In addition to the wide commercial availability of such antibodies, persons skilled in the art will know how to generate such cross-linking antibodies, either polyclonal or monoclonal, using techniques that are now conventional in immunology and molecular biology.

Furthermore, Applicant respectfully submits that rather than provide a generic or a sub-generic disclosure, as asserted by the Examiner, the Examples provide a disclosure of particular species of the claimed genus of cross-linking antibodies. In view of the foregoing in respect of widely available and readily generated anti-isotype antibodies as further species of such genus, such description is adequate support for the genus as a whole. Accordingly, Applicant respectfully submits that the cross-linking antibodies claimed in claims 4 and 20 are disclosed and adequately supported by the specification for purposes of satisfying the written description requirement of 35 U.S.C. 112, first paragraph. Applicant therefore respectfully requests the Examiner to reconsider and withdraw the written description rejection of claims 4 and 20 under 35 U.S.C. 112, first paragraph.

#### **Rejection Under 35 U.S.C. 112, First Paragraph (Enablement)**

In item number 5 beginning on page 5 of the Office Action the Examiner maintained his previous rejection of claims 4 and 20 under 35 U.S.C. 112, first paragraph, because the specification, while enabling anti-hamster Ig and rabbit anti-mouse Ig as “an antibody that binds to the monoclonal antibody and induces [the] cross-linking of a plurality of PSGL-1 antigens on the surface of [the] cell”, allegedly does not reasonably provide enablement for any “antibody that binds to the monoclonal antibody and induces [the] cross-linking of a plurality of PSGL-1 antigens on the surface of [the] cell”. On page 6 of the Office Action the Examiner asserted that the specification does not provide sufficient direction and guidance as to the nature of antibodies that can induce cross-linking in vivo. Further on page 6 the Examiner conceded that cross-

linking antibodies in vivo may be accomplished by various antibody constructs, including multimeric antibodies, or antibodies that bind anti-PSGL-1 antibodies that are *not* hamster antibodies [original emphasis]. Finally, also on page 6 of the Office Action, the Examiner concluded that without sufficient guidance, making and using an “antibody that binds to the monoclonal antibody and induces [the] cross-linking of a plurality of PSGL-1 antigens on the surface of [the] cell” other than the anti-hamster/mouse Ig disclosed in the specification as filed as the antibody in the claimed methods would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Applicant respectfully disagrees and requests the Examiner to reconsider and withdraw this rejection of claims 4 and 20 under 35 U.S.C. 112, first paragraph.

The Examiner has indicated his acknowledgement of an enabling disclosure for two examples of cross-linking antibodies, viz., anti-hamster Ig and rabbit anti-mouse Ig. Applicant respectfully submits that further enablement is not required, at least for the following reasons. First, as mentioned above in connection with the written description rejection, persons skilled in the art reading the disclosure of the instant invention will recognize that the claimed genus of cross-linking antibodies includes, without limitation, any suitable anti-isotype antibody. Thus in connection with a monoclonal hamster anti-PSGL-1 antibody of IgG isotype, the skilled person would recognize that an antibody of non-hamster origin that is specific for hamster IgG would reasonably be expected to cross-link PSGL-1 antigens previously bound by monoclonal hamster anti-PSGL-1 antibody of IgG isotype. Without meaning to be limiting, persons of skill in the art would recognize that such antibody of non-hamster origin may be of mouse, rat, guinea pig, rabbit, goat, sheep, horse, human, etc., origin. Such types of antibodies are generally widely available from any of several commercial sources. Accordingly, Applicant respectfully submits that the claimed methods would not be so unpredictable and the experimentation left to those skilled in the art would not be so necessarily, and improperly, extensive and undue, as to fail to enable the skilled person to make and use the invention as claimed.

Second, also as mentioned above in connection with the written description rejection, persons skilled in the art reading the disclosure of the instant invention will know how to

generate such cross-linking antibodies, either polyclonal or monoclonal, using techniques that are now conventional in immunology and molecular biology. The fact that some amount of experimentation may be required does not automatically negate enablement. Rather, an enablement rejection requires that the amount of experimentation to be performed by a person skilled in the relevant art must be an undue amount of experimentation. Applicant submits that the level of skill in the art for generating antibodies against identified antigens is very high, e.g., Ph.D.-level molecular biologists and immunologists. Where, as in the instant application, the experimentation involves raising antibodies against identified antigens, e.g., against monoclonal antibodies, no more than a reasonable amount of experimentation would be required. Accordingly, Applicant respectfully submits that the claimed methods would not be so unpredictable and the experimentation left to those skilled in the art would not be so necessarily, and improperly, extensive and undue, as to fail to enable the skilled person to make and use the invention as claimed.

In view of the foregoing, Applicant respectfully requests the Examiner to reconsider and withdraw the enablement rejection of claims 4 and 20 under 35 U.S.C. 112, first paragraph.

### **Rejection Under 35 U.S.C. 102**

Beginning with item number 6 on page 6 of the Office Action and continuing through item number 7 beginning on page 7 of the Office Action, the Examiner rejected claims 1, 3, 6, 10-12, 17, 19, and 22-24 under 35 U.S.C. 102(b) for alleged anticipation by Larsen et al. (US Patent No. 5,840,679; "Larsen") essentially for reasons of record and further in view of Chen et al. (*Blood* 104:3233-42 (2004); "Chen"). In respect of Larsen, the Examiner suggested that it is difficult to ascertain the distinctions between the claimed and prior art methods, which inhibit T cell-mediated immune responses with PSGL-1-specific antibodies, where Larsen is silent about depletion of T cells, generally, and about "inducing a signal transduction [pathway] that results in the death of the T cell thereby reducing a T cell-mediated immune response in the individual, more particularly. The Examiner invited Applicant to provide clarity and objective evidence as to distinctions between properties of anti-PSGL-1 antibodies of Larsen and the instant anti-

PSGL-1 antibodies, as well as the mechanism of action by which the administration of anti-PSGL-1 antibodies, as claimed, can reduce T cell-mediated immune responses. Furthermore, on page 9 of the Office Action the Examiner indicated it is difficult for the Examiner to determine whether: Applicant has discovered a new mode of action of anti-PSGL-1 antibodies; Applicant has discovered a new epitope specificity of apoptosis-inducing anti-PSGL-1 antibodies; Applicant is relying on secondary cross-linking agents/antibodies to accomplish this newly discovered mode of action; and/or whether administration of anti-PSGL-1 antibodies even in Applicant's model operate via apoptosis in vivo in the absence of secondary cross-linking agents/antibodies.

In respect of Chen, the Examiner suggested on page 7 of the Office Action that Chen teaches that PSGL-1 mediated death via PSGL-1-specific antibodies is stage dependent in that it affects mature activated T cells, and that therefore (according to the Examiner) Applicant's reliance on "inducing a signal transduction pathway that results in the death of the T cell thereby reducing a T cell-mediated immune response in the individual" appears not based on the nature of the anti-PSGL-1 antibody but rather based on the presence of PSGL-1 expressing mature activated T cells.

For reasons set forth below, Applicant respectfully disagrees and requests the Examiner to reconsider and withdraw the rejection of claims 1, 3, 6, 10-12, 17, 19, and 22-24 under 35 U.S.C. 102.

Applicant wishes first to reiterate that independent claims 1 and 17 are currently amended to specify that the antibody is an *apoptosis-inducing anti-PSGL-1 antibody*, and further to specify that the binding of the antibody or antigen-binding fragment thereof to PSGL-1 on the surface of the T cell (or NK cell) induces *apoptosis* of the T cell (or NK cell).

In response to the Examiner's invitation, Applicant submits herewith a Declaration Under 37 C.F.R. 1.132 made by Dr. Shi-Yao Lin, M.D., Ph.D., current President of AbGenomics Corporation, the assignee of record. Applicant respectfully submits that Dr.

Lin's declaration further addresses concerns of the Examiner raised in connection with both Larsen and Chen.

More particularly, Dr. Lin's declaration makes clear that certain anti-PSGL-1 antibodies, but not others, are capable of inducing apoptosis of mature, activated T cells. Data presented and discussed in the declaration by Dr. Lin indicates that certain anti-PSGL-1 antibodies bind to PSGL-1 expressed on mature, activated T cells, without inducing apoptosis of those cells. Conversely, other data presented and discussed in the declaration by Dr. Lin indicates that certain anti-PSGL-1 antibodies bind to PSGL-1 expressed on mature, activated T cells and do induce apoptosis of those cells, without interfering with the ability of PSGL-1 to interact with various selectins. In respect of Larsen, then, it will be appreciated that Dr. Lin's declaration makes clear that the prior art methods and anti-PSGL-1 antibodies would not necessarily and inevitably involve anti-PSGL-1 antibodies that are capable of inducing apoptosis of T cells, as claimed. Larsen discloses both neutralizing and non-neutralizing anti-PSGL-1 antibodies, wherein the former but not the latter are disclosed to interfere with the ability of PSGL-1 to interact with various selectins. Larsen, column 18, lines 57-65. However, as appreciated by the Examiner, Larsen makes no teaching whatsoever concerning apoptosis. Since Larsen is silent concerning apoptosis, and since not all anti-PSGL-1 antibodies are capable of inducing apoptosis (as specified by the instant claims), Larsen clearly does not and cannot anticipate the claimed methods.

It should be noted that Dr. Lin's declaration also makes clear that certain anti-PSGL-1 antibodies are capable of inducing apoptosis of mature, activated T cells, but not others, even in the presence of suitable cross-linking antibody. More particularly, data presented and discussed in the declaration by Dr. Lin indicates that certain anti-PSGL-1 antibodies bind to PSGL-1 expressed on mature, activated T cells but do not induce apoptosis of those cells, even in the presence of cross-linking antibodies specific for the anti-PSGL-1 antibodies. See Figure B(1a) - Figure B(2b). In addition, other data presented and discussed in the declaration by Dr. Lin indicates that certain anti-PSGL-1 antibodies bind to PSGL-1 expressed on mature, activated T cells and, in the presence of cross-linking antibodies specific

for the anti-PSGL-1 antibodies, induce apoptosis of those cells, without interfering with the ability of PSGL-1 to interact with P-selectin. See Figure C(1a) - Figure C(2b).

Applicant believes that the claimed *in vivo* methods involve cross-linking of suitable anti-PSGL-1 antibodies to induce apoptosis of T cells bound by the anti-PSGL-1 antibodies. Applicant further asserts that such cross-linking can and does occur *in vivo* in absence of cross-linking antibodies. Applicant asserts that such cross-linking can result from binding to the anti-PSGL-1 antibodies by other cells of the treated host, e.g., via Fc receptors (FcR). Applicant therefore is not necessarily “relying upon secondary cross-linking agents/antibodies” to accomplish apoptosis induction (see page 9 of Office Action). Furthermore, Applicant therefore also asserts that administration of anti-PSGL-1 antibodies can and does induce apoptosis of T cells *in vivo*, in the absence of administering secondary cross-linking agents/antibodies, as claimed (see page 9 of Office Action).

It should be noted that Larsen makes no disclosure at all concerning cross-linking of anti-PSGL-1 antibodies by any means. Larsen clearly does not anticipate the claimed methods because Larsen has no appreciation of apoptosis-inducing anti-PSGL-1 antibodies and no appreciation of any possible role for cross-linking of apoptosis-inducing anti-PSGL-1 antibodies. In contrast, the instant claims require the use of apoptosis-inducing anti-PSGL-1 antibody. As is evident from Dr. Lin’s declaration, such antibodies can be selected from a panel of antibodies that bind to anti-PSGL-1. However, Larson does not teach such selection, and, accordingly, as is also evident from Dr. Lin’s declaration, the prior art methods and anti-PSGL-1 antibodies would not necessarily and inevitably involve anti-PSGL-1 antibodies that are capable of inducing apoptosis of T cells, as claimed.

In respect of Chen, Applicant agrees with the Examiner that Chen teaches that PSGL-1 mediated death via PSGL-1-specific antibodies is stage dependent in that it affects mature activated T cells. However, Applicant respectfully disagrees with the Examiner’s position that Applicant’s reliance on “inducing a signal transduction pathway that results in the death of the T cell thereby reducing a T cell-mediated immune response in the individual” (now,

“inducing apoptosis”) is not based on the nature of the anti-PSGL-1 antibody but rather is based on the presence of PSGL-1 expressing mature activated T cells. It is respectfully submitted that the teaching of Chen is not mutually exclusive to the notion that induction of apoptosis of mature T cells is based on use of certain anti-PSGL-1 antibodies, viz., apoptosis-inducing anti-PSGL-1 antibodies, as claimed, rather than other anti-PSGL-1 antibodies. As stated above, Dr. Lin’s declaration clearly points out that that certain anti-PSGL-1 antibodies, but not others, are capable of inducing apoptosis of mature T cells. Thus it is respectfully submitted that the Examiner is incorrect to conclude from Larsen, further in view of Chen, that the prior art anticipates the instant claims because Applicant’s reliance on “inducing apoptosis” is misplaced. The instant application clearly discloses the use of apoptosis-inducing anti-PSGL-1 antibodies to induce apoptosis of PSGL-1-expressing T cells. The prior art neither discloses the claimed methods nor does it negate the claimed methods, as the Examiner appears to suggest.

In view of the foregoing, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 1, 3, 6, 10-12, 17, 19, and 22-24 under 35 U.S.C. 102.

### **Rejection Under 35 U.S.C. 103**

In item number 8 on page 10 of the Office Action the Examiner rejected claims 1, 3, 6, 10-113, 19, 20, and 22-25 under 35 U.S.C. 103(a) as being unpatentable over Larsen (*supra*) in view of Trembleau et al. (*J Immunol* 163:2960-8 (1999); “Trembleau”), Yago et al. (*J Immunol* 161:1140-5 (1998); “Yago”), Hirata et al. (*J Exp Med* 192:1669-75 (2000); “Hirata”), and Cobbold et al. (U.S. Patent No. 6,056,956; “Cobbold”) and as further evidenced by Chen (*supra*) essentially for the reasons of record. More particularly, the Examiner asserted on page 10 of the Office Action that there is insufficient objective evidence that the treatment [with] anti-PSGL-1 antibodies in the prior art [does] not result in the claimed cell death of T cells via cross-linking (e.g., via Fc-FcR binding) and/or the presence of PSGL-1 expressing mature activated T cells during the administration of PSGL-1 specific antibodies. Applicant respectfully disagrees

and requests the Examiner to reconsider and withdraw the rejection of claims 1, 3, 6, 10-113, 19, 20, and 22-25 under 35 U.S.C. 103.

As pointed out above in connection with the rejection under 35 U.S.C. 102, Larsen does not teach, expressly or inherently, all elements of the pending claims. More particularly, Larsen does not teach, expressly or inherently, the use of apoptosis-inducing anti-PSGL-1 antibodies. Furthermore, neither does Larsen suggest or provide motivation to substitute apoptosis-inducing anti-PSGL-1 antibodies for the neutralizing or non-neutralizing antibodies disclosed in Larsen. In addition, none of Trembleau, Yago, Hirata, and Cobbold suggests that an antibody that binds PSGL-1 induces apoptosis of cells expressing PSGL-1 on their surface, thereby to reduce an immune response or induce apoptosis of a T cell or NK cell. As previously acknowledged by the Examiner, each of these secondary references suggests, at best, only antagonizing PSGL-1 function as a means to regulate an immune response. Therefore none of Trembleau, Yago, Hirata, and Cobbold furnishes what is absent from Larsen in order to sustain the obviousness rejection made by the Examiner. Chen postdates the instant application. Given the inability of the proposed combination of prior art references to render obvious the instant claims, Chen does not alter the conclusion that the instant claims are not obvious in view of the prior art.

### **Provisional Rejection Based on Double Patenting**

Beginning with item 9 on page 10 and continuing through item 10 on page 11 of the Office Action, the Examiner provisionally rejected claims 1, 3, 4, 6, 10-13, 17, 19, 20, and 22-25 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 8, 9, 12-15, 19-22, 23, 26, 30, 31, and 34-38 of copending and commonly assigned application USSN 10/662,906. Without meaning to signal agreement with the Examiner's characterization of the claims of either application in respect of the other, Applicant simply acknowledges the Examiner's rejection.

Since the rejection is provisional, Applicant respectfully requests that this rejection be held in abeyance until such time as the present application or cited co-pending application issues as a patent, at which time Applicant will cancel or amend any identical claims in the remaining application.

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

Respectfully submitted,

By 

Alan W. Steele, M.D., Ph.D.

Registration No.: 45,128

WOLF, GREENFIELD & SACKS, P.C.

Federal Reserve Plaza

600 Atlantic Avenue

Boston, Massachusetts 02210-2206

(617) 646-8000

Dated: January 30, 2007  
WGS Date: 01/31/2007